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Assessing the Impact of Risk Evaluation and Mitigation Strategies with Elements to Assure Safe Use on Patient Access

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Background

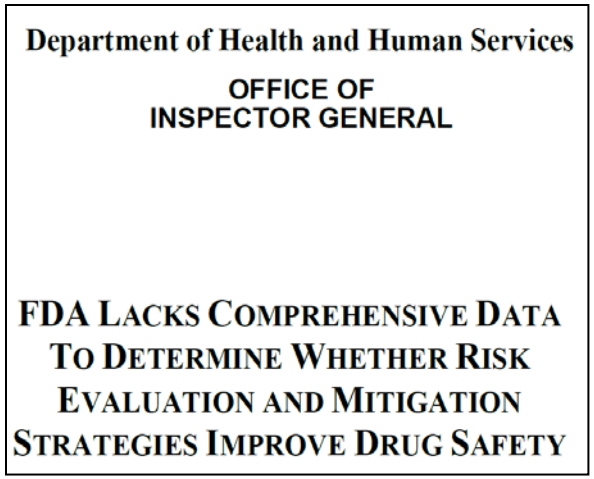
- Authorized FDA to require REMS
  - For drug with known or suspected safety concerns
  - When necessary to ensure benefits outweigh risks

- REMS categories and frequency of use
  - Medication guides: 41 (51%)
  - Communication plans: 33 (41%)
  - Elements to assure safe use (ETASU): 43 (53%)
    - Mandatory training or certification for prescribers and pharmacies
    - Person, place, and time restrictions on dispensing
    - Patient follow-up and testing
  - Implementation systems: 37 (46%)

Unknown Impact of ETASU REMS

- Pre-REMS, RiskMAP case study: isotretinoin (Accutane) iPledge
  - Use two forms of contraception
  - Monthly pregnancy tests
  - Decrease in number of new initiators of isotretinoin
    - 113,578 vs. 77,072 (24-months before vs. after adoption)
  - Small but significant increase in concomitant use (1.3%, p=0.02)

-Pinheiro et al., Pharmacoepidemiol Drug Saf, 2013.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FDA LACKS COMPREHENSIVE DATA TO DETERMINE WHETHER RISK EVALUATION AND MITIGATION STRATEGIES IMPROVE DRUG SAFETY

- Unresolved Questions
  - Do ETASU REMS reduce patient access?
  - If so, to what extent and among whom?

Empirical Study of ETASU REMS

- Requirement: control frame-ETASU REMS imposed or removed post-approval

- Case study: thrombopoietin agonists
  - Eltrombopag (Promacta; GlaxoSmithKline; oral tablet)
  - Romiplostim (Nplate; Amgen; subcutaneous injection)

-Sarpatwari et al., Clin Pharmacol Ther, 2015.

- Relevant drug history
  - August (romiplostim) and November (eltrombopag) 2008
    - FDA approval for primary immune thrombocytopenia (ITP)
    - Imposition of ETASU REMS at time of drug approval

- December 2011: FDA removal of ETASU REMS from both drugs

- Growing evidence for eltrombopag in HCV-associated thrombocytopenia
  - November 2007: Phase II trial of 57 patients on active therapy for 4 weeks
  - November 2011: Phase III trial abstract confirms efficacy
  - November 2012: FDA approval of indication

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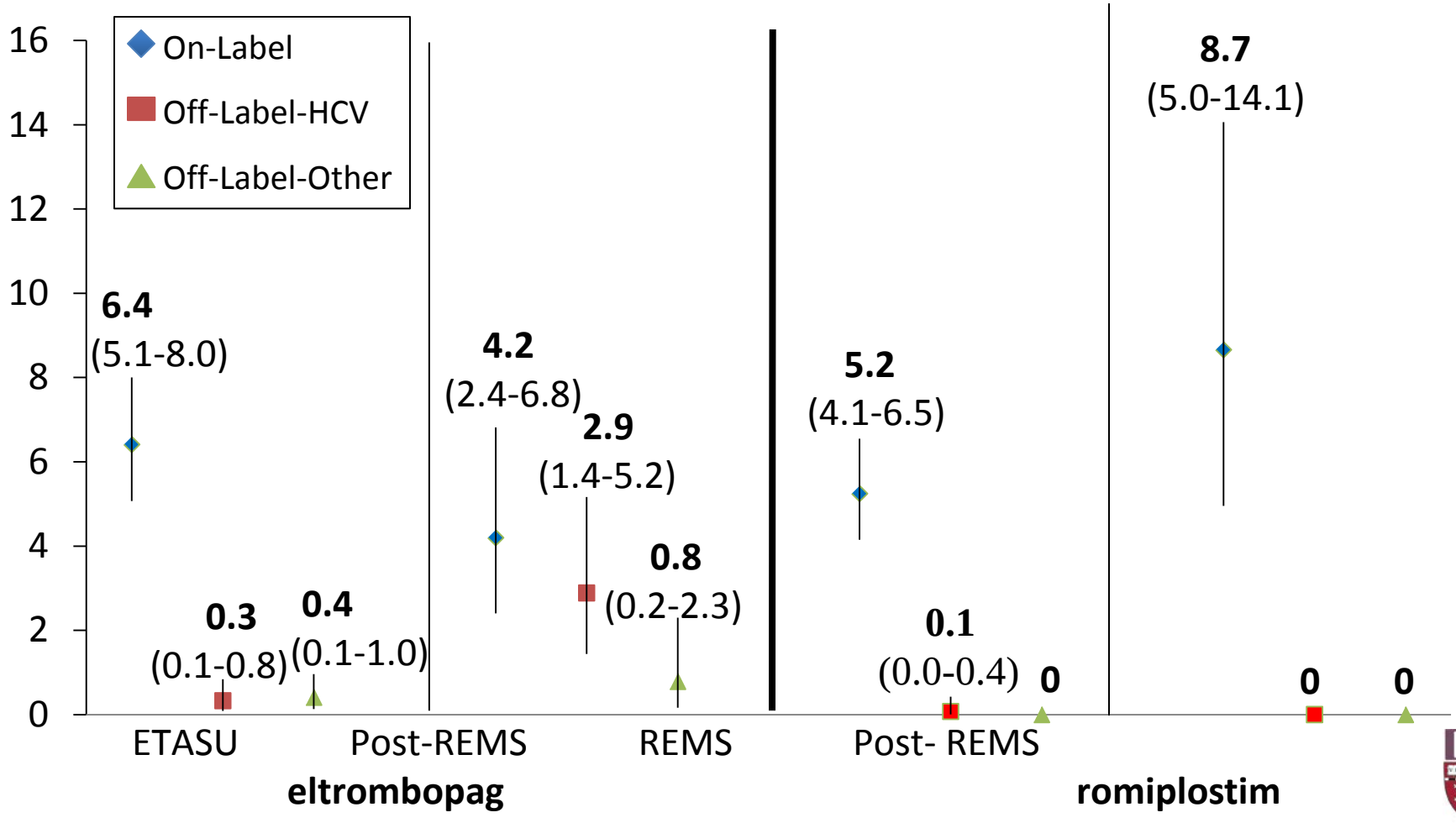
Study Design and Analyses

- Study type: retrospective cohort study with time series analysis
- Source: Optum Research Database (UnitedHealth)
- Population: adult (>18 years) initiators of eltrombopag or romiplostim before and after 2011 removal of ETASU REMS
- Usage categories: based on validated ICD-9 codes ± 180 days initiation
  - On-Label: 287.3 or 287.31
  - Off-Label/HCV: 070.41, 070.51, 070.54, or V02.62 & Off-Label/Other
- Before and after ETASU REMS removal: 2008-2012
  - Incidence rates
  - Poisson model: ratio of incidence rate ratios (IRR)
    - Off-Label/HCV to On-Label initiation
    - Off-Label/Other to On-Label initiation

Results

	N or Mean (% or SD)		N or Mean (% or SD)	
Time Period	**ETASU**	**Post-ETASU**	**ETASU**	**Post-ETASU**
Total	87 (100)	30 (100)	70 (100)	33 (100)
Age (Years)	49.7 (±15.6)	52.1 (±16.6)	51.9 (±13.7)	50.3 (±14.2)
Female	50 (57.5)	14 (46.7)	32 (45.7)	15 (45.5)



Results Cont'd

	Eltrombopag			Romiplostim		
Time	**ETASU** N (%)	**Post-ETASU** N (%)	**Ratio of IRR** (95% CI)	**ETASU** N (%)	**Post-ETASU** N (%)	**Ratio of IRR** (95% CI)
On-Label	78 (89.7)	16 (53.3)	--	69 (98.6)	33 (100)	--
Off-Label-HCV	4 (4.6)	11 (36.7)	13.4 (3.8-47.5)	1 (1.4)	0 (0)	~0 (0-[~∞])
Off-Label-Other	5 (5.7)	3 (10.0)	2.9 (0.6-13.5)	0 (0)	0 (0)	2.1 (0-[~∞])

- Insurance policies
  - eltrombopag
    - Prior authorization added in the post-ETASU REMS period
      - Expectation: decreased off-label use (not observed)
  - romiplostim: no prior authorization throughout

- Concomitant use with telaprevir or boceprivir
  - Only 3 of 11 (27.3%) incident uses in the post-ETASU REMS period

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Conclusions and Limitations

- Conclusions
  - Under ETASU REMS, nearly exclusive On-Label initiation of both drugs
  - After ETASU REMS, jump in Off-Label/HCV eltrombopag initiation
    - ETASU REMS might prevent off-label use
    - But evidence for Off-Label/HCV use present under ETASU REMS
  - No change in Off-Label/HCV romiplostim initiation
    - Possible reasons
      - Not tested in HCV
      - Subcutaneous injection
      - ICD-9 code required for claims

- Limitations
  - Greater sample size needed for more rigorous analytic techniques
  - External validity: exist a range of ETASU REMS programs

Future Work

- Methodological application
  - Incorporation of condition-specific health outcomes
  - Possible extrapolation to similar ETASU REMS programs
    - Considerations
      - Similarities in treatment effectiveness and alternatives
      - Similarities in prevalence and severity of condition

- Other aspect of ETASU REMS affecting patient access
    - Measuring delayed generic entry
      - Restricted distribution schemes
      - ETASU REMS patenting

Using a Drug-Safety Tool to Prevent Competition

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-New Engl J Med, 2014.

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